Scientific Abstract

Intramuscular injection of naked plasmid DNA results in myocyte uptake of injected DNA and subsequent expression of encoded genes in multiple animals models. Myocyte expression of immunogenic molecules, including tumor antigens, directed by injected plasmid DNA elicits humoral and cellular immune responses, with resultant immunoprotection against tumor challenge in animal models. Phase I clinical trials of a variety of polynucleotide vaccines have demonstrated no significant adverse events.

MART-1, melanoma antigen recognized by T cells-1, is recognized by tumor infiltrating lymphocytes and peripheral blood lymphocytes from many melanoma patients. Furthermore, in vitro stimulation of peripheral blood lymphocytes from normal donors or melanoma patients with an HLA-A2 restricted 9-mer peptide from this antigen generates melanoma-reactive cytotoxic T cell lines. Consequently, MART-1 is currently being targeted in multiple defined antigen immunization trials. Based upon the substantial risk of disease recurrence in defined subsets of patients with resected melanoma, the lack of effective therapy for recurrent melanoma, and the apparent role of MART-1 as a tumor regression antigen; we propose to conduct a dose escalation study of a plasmid DNA vaccine encoding MART-1 in patients with resected Stage IIb, III or IV melanoma. Such patients have a 50% or greater risk of relapse and death due to melanoma within the next ten years. To the best of our knowledge, this trial will be the first to use the full-length MART-1 cDNA delivered by a non-viral vector. This strategy provides several advantages including effective booster administration which is not limited by development of immunity to a viral vector. Concomitant administration of a polynucleotide vaccine encoding HBsAg will be utilized as a positive control for immune response. Therefore, we have cloned the cDNA's for MART-1 and HBsAg into separate plasmids consisting of an identical plasmid backbone and differing only in the cDNA insert. The MART-1 plasmid and HBsAg plasmid will be injected into opposite deltoid muscles to eliminate any negative affects which the HBsAg cDNA might have on the immune response to MART-1 if the two cDNA's were delivered to the same site. This strategy should circumvent the following two concerns associated with co-delivery of the tumor antigen and HBsAg within the same plasmid:

1) diminished levels of tumor antigen expression within myocytes due to competition between the two CMV promoters of a dual expression construct

2) shortened survival of transduced myocytes expressing the tumor antigen due to immune-mediated destruction secondary to concomitant expression to HBsAg.

We propose to evaluate this vaccine in patients with minimal residual disease (i.e. the adjuvant setting) because evaluation of such an immunization strategy in terminally ill patients with widely disseminated melanoma may lead to the inappropriate rejection of a treatment which could play a potentially important role in the adjuvant setting.